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INSTRUCTIONS TO AUTHORS

The Journal considers any original research that advocates change in, or illuminates, clinical practice. The journal also publishes interesting and informative reviews and opinion pieces on any topic connected with clinical practice. Manuscripts must be solely the work of the author(s) stated, not have been published previously elsewhere, and not be under consideration by another journal. All papers should be written to be clearly understandable to the journal's readers in a wide range of specialties and countries. Diagrams, figures, and photographs should be used to supplement and enhance the text.

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Title page should consist of: (1) Title of the article (2) Complete name and profession title (3) Institution Name (4) Address of correspondence of main author.

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Illustration

Illustration, which is enclosed in the article can be hand-made picture, photograph, table or graph. Hand-made picture are made by black ink on white paper. Photograph can be enclosed in the article or as a file of scan result. Tables are made complete, including the parts of:

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Ethics

In reporting / writing experiments result with certain object (i.e. patient's names, or institution or others), should never mention about identity or other characteristic that describes that object. The Editorial Board reserves the right to carry out editorial change if it is considered important.

CLINICAL CHARACTERISTICS AND DISEASE SEVERITY

Caring patients with chronic illnesses or acute severe diseases often drives physicians to find clinical characters that may predict outcome or describe severity of disease. Sorting patients with poorer prognosis or with particular risk factors will facilitate application of aggressive treatment in this high risk group of patients.

In this 2nd edition of Acta Interna, we include 4 original articles that explore the certain clinical characteristic related to severity of disease; 1 original article related to particular side effect of cancer chemotherapy; and one case report of complication of chronic end stage disease.

One article from gastroentero hepatology highlighted correlation of Cystatin C, a non-glycosylated protein of 13 kDa cystatin super family, in severity of cirrhosis. Cystatin C- which is recommended to assess declining of renal function- is correlated with severity of cirrhosis (which is measured by Model of End Stage Liver Disease [MELD]). MELD itself has been commonly used to measure severity of cirrhosis patients using calculation of 3 clinical characters of serum creatinin, total bilirubin, and INR. In this study higher serum Cystatin C level was correlated with higher MELD score or more severe condition. The second original article came from cardiology area. This study correlated serum level of Matrix Metalloproteinase-9 (MMP-9), an extracellular matrix degrading enzyme, with severity of muscle damage in acute coronary syndrome which was measured with serum Troponin-I level. Some clinical characteristics failed to be proved to have significant role in assessing disease severity as reported by our third article from pulmonology, which could not prove the role of serum magnesium level in predicting severity of asthma measured with Peak Expiratory Flow. Our 4th article reported that higher level of potassium on admission and neurological symptoms were associated with mortality in Leptospirosis. However, all these four original articles used cross sectional design and retrospective studies which owned limitation in drawing conclusion.

We involved another original article from hemato-oncology area reporting significant declining of cognitive function among breast cancer women received antracyclin based adjuvant chemotherapy. A case report of a chronic kidney disease patient experienced complication of acute coronary syndrome despite of undergone routine hemodialysis captured quality of care and the role of secondary prevention approach in chronic disease management. This case report will close our 2nd edition.

Sincerely Yours,

Editors

CORRELATION BETWEEN CYSTATIN C TO DISEASE SEVERITY OF CIRRHOSIS BASED ON MODEL OF END STAGE LIVER DISEASE SCORE

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ABSTRACT

***Background**: Cirrhosis patients with renal failure are at high risk for death and reduced survival as compared with those without renal failure, and have poor prognosis. Some studies have suggested that cystatin C did more accurate than creatinine to detect glomerulus filtration rate (GFR) in patients with cirrhosis. Model of End Stage Liver Disease (MELD) score can be used in patients with cirrhosis with variously widely severity disease and etiologies. Until now, there is no study about correlation between levels of cystatin C to disease severity in cirrhosis based on MELD score.*

***Objective**: This present study was to investigate the correlation between levels of cystatin C with disease severity in cirrhosis based on MELD score.*

***Method**: Study design was cross sectional study. This study was conducted at Gastoenterohepatology outpatient clinic and Internal Medicine ward of Dr Sardjito General Hospital, Yogyakarta. Inclusion criteria were patients with cirrhosis diagnosed by clinical criteria, laboratory and USG finding, age ⩾ 18 years, had complete medical record and obtained informed consent. Exclusion criteria were chronic kidney disease, sepsis, hepatocellulare carcinoma, used high doses of steroid, had thyroid dysfunction, hypertension and diabetes mellitus.*

***Result**: The mean of cystatin C based on categorical MELD score were MELD <10 = 0.93±0.19 mg/l; MELD 10-19=1.08±0.26 mg/l; MELD 20-29 = 1.25±0.27 mg/l; MELD 30-39 = 2.49 mg/l and MELD >40 = 2.43 mg/l; (p=0.013; 95% CI 0.000-0.061). There was a significant correlation between cystatin C to MELD score as demonstrated by p=0.000 and r=0.485.*

***Conclusion**: Our data suggested a significant correlation with medium strength between cystatin C to severity disease of cirrhosis based on MELD score.*

***Keywords**: cirrhosis, cystatin C, MELD score*

INTRODUCTION

Impaired renal complication from cirrhosis is challenging. Liver cirrhosis patients with renal impairment are at high risk for mortality and reduced survival when compared with liver cirrhosis without renal impairment[1]. Decline in renal function in patients with liver cirrhosis showed a poor prognosis[2]. Glomerular filtration rate (GFR) is a direct measure of function renal which is impaired, before the onset of symptoms and damage associated with the severity of renal glomerular impairment [3]. Glomerular filtration rate is a method which is considered accurate in estimating the renal function[4].

The use of endogenous substances such as creatinine as a marker has been commonly used as a biochemical marker of GFR. Individual variation of creatinine is low, however its oncentration as a determinant of GFR depends on muscle mass, protein intake, age, gender, race, and extra-renal metabolism. All of this will affect the rate of GFR[5].

Research has shown that Cystatin C, a non-glycosylated protein of 13 kDa cystatin super family, was more accurate than creatinine in assessing GFR decline in patients with liver cirrhosis[6]. Cystatin C has a significant relationship in predicting GFR than creatinine and was not influenced by age and body mass so that the measurement of cystatin C is recommended to

detect renal impairment in patients with liver cirrhosis[5].

Classification of Child-Turcotte-Pugh (CTP) has become a benchmark for more than 30 years to asses the prognosis of liver cirrhosis. Score of Model of End Stage Liver Disease (MELD) is the best alternative from the CTP score. Score of MELD has been established as a promising tool to replace the CTP score and overcome its limitations. Score of MELD is useful in patients with liver cirrhosis with broad range of disease severity and etiology of cirrhosis, even in patients who do not have clear causes[3].

SUBJECTS AND METHODS

The research method used in this study is cross sectional. The study was conducted in the Gastroenterohepatology outpatient clinic and ward of Internal Medicine Dr. Sardjito General Hospital, Yogyakarta. Research conducted during October 2009 to March 2010. Research target population is patients with liver cirrhosis.

Inclusion criteria were patients with a diagnosis of liver cirrhosis based on clinical criteria, laboratory and liver ultrasound, patient age adults (⩾ 18 years), have a complete medical record and signed research consent. Exclusion criteria were patients with renal failure coincident with liver cirrhosis, liver cirrhosis patients who had sepsis, liver cirrhosis patients with hepatocellular carcinoma (HCC), patients with liver cirrhosis who also used high doses corticosteroids, patients with liver cirrhosis who have thyroid dysfunction, patients with hypertension and patients with diabetic mellitus.

Patients with liver cirrhosis at the Gastroenterehepatology outpatient clinic and treated at the Internal Medicine Ward of Dr. Sardjito General Hospital Yogyakarta were recorded for their baseline identity and history on the use of corticosteroid medications, history of kidney disease, thyroid, hypertension, diabetic mellitus, colorectal malignancy, prior to physical examination.

Subjects who met inclusion criteria underwent venous blood sampling as much as ± 10cc, 5cc for examination of albumin, bilirubin, creatinine and INR in the Laboratory of Clinical Pathology of Dr. Sardjito General Hospital, Yogyakarta and 5cc for cystatin C examination in the Prodia private laboratory.

DATA ANALYSIS

Characteristics data of the study subjects are presented in the figures mean and standard deviation. Normal distribution of variables is determined by Shapiro-Wilk test. Correlation between levels of cystatin C and score of MELD using Spearman correlation test due to the abnormal data distribution. Statistically significant differences determined by the value of $p < 0.05$ and confidence interval (CI) 95%.

RESULTS

Research done by sequentially sampling and found 48 subjects with basic characteristics displayed in the table 1.

Tabel 1. Baseline Characteristics of The Patients

Variables		Median (minimum-maximum)
Sex		
Male (n) (%)	35 (72.9)	
Female (n) (%)	13 (27.1)	
Age (years)	53.10±11.90	
Ascites		
No (n) (%)	21 (43.8)	
Yes (n) (%)	27 (56.2)	
Albumin (g/dl)	2.67±0.7.	
Bilirubin (mg/dl)	3.31±3.85	2.06 (0.36-22.40)
Creatinine (mg/dl)	1.09±0.32	1.08 (0.44-2.23)
INR	1.90±2.45	1.36 (0.92-17.90)
MELD score (n) (%)		
<10	13 (27.1)	
10-19	29 (60.4)	
20-39	4 (8.3)	
30-39	1 (1.21)	
>40	1 (1.21)	
MELD score	14.90±7.38	14.10 (3.01-44.38)
Cystatin C (mg/l)	1.11±0.38	1.01 (0.67-2.49)

Table 2. Comparison of Clinical and laboratory groups of Cystatin C≤ 0.96 mg/l and Cystatin C > 0.96 mg/l

Variable	Cystatin C > 0.96 mg/l (n=26)	Cystatin C ≤0.96 mg/l (n=22)	p	95%CI
Sex				
Male (n) (%)	19 (39.6)	16 (33.3)	0.978*	-1.295-1260
Female (n) (%)	7 (14.6)	6 (12.5)		
Age (years)	54.54±12.78	51.41±10.82	0.370^s	-10.08-3.820
Albumin (mg/dl)	2.53±0.69	2.89±0.81	0.104^s	-0.080-0.790
Ascites				
No (n) (%)	10 (20.8)	11. (22.9)	0.442*	-0.680-1.620
Yes (n) (%)	16 (33.3)	11 (22.9)		
MELD score	17.84±8.20	11.43±4.29	0.000*	0.000-0.061

Table 2 showed that gender, age, albumin and ascites was not significantly different and only MELD scores difference between groups of cystatin C showed significant differences between groups of Cystatin C.

Table 3. Difference Average Concentrations of Cystatin C by the score of MELD

	MELD <10	MELD 10-19	MELD 20-29	MELD 30-39	MELD >40	p	95% CI
Cystatin C	0.93±0.19	1.08±0.26	1.25±0.27	2.49	2.34	0.013*	0.000-0.061

Score of MELD correlation test on levels of cystatin C obtained p=0.000 and r=0.485 performed linear regression to see the relationship score of MELD with levels cystatin C and obtained the equation C=0.56 + (0.04 x score of MELD) with R-square 0.51.

DISCUSSION

In this study, there were more males than females with cirrhosis. The percentage of male patients was higher than previous studies which reported 67%, 55%, 64%, 63.7%.[9-12] Two reports showed that male patients had been reported to be more frequent hospitalized with end stage live disease as many as 55% and 66% [13-14]. However, a systematic review showed a median age of patients with liver cirrhosis of 54 (44-67) years and 67% were female[15].

A study in the UK reported the incidence of liver cirrhosis to be 14.55 per 100,000 populations that had been increased from 12.05 per year to 16.99 per 100,000 people per year. The incidence of liver cirrhosis is 50% higher in men than women (relative risk 1.52, 95% CI 1.42-1.63). One of the main causes was the more frequent consumption of alcohol in men than in women.

The mean age of these patients was in accordance to the range of previous studies. Some previous studies found the average age of patients with cirrhosis at 56 years old (range 36-70); 50 ± 12.5 years (18-86) years old; 56.7 ± 10.5 years; 62.3 ± 12.9 (range 29-87) years old; 61 (50-69) years; 55±10 (29-80) years; median age 50 (22-75) years old; 52.9 ± 12.5 years, median 55.5 (20-71) years old [9-13, 18-20].

Our study found the subject of liver cirrhosis with ascites more than without ascites which showed that most subjects had advanced liver disease. Previous studies found 69%, 94%, 53%, 20% of patients with liver cirrhosis had ascites[9,11,19,21]. The results of this study were equal to 3 previous studies in which the percentage of the liver cirrhosis with ascites was more frequent than without ascites. This study showed that most subjects had cirrhosis of the liver disease with advanced stage. The result

of this study was different from 2 previous studies that reported the incidence of liver cirrhosis without ascites to be more frequent than with ascites.

Average concentrations of albumin in this study showed hypoalbuminemia and lower than the previous studies. The mean albumin in this study showed a low value. The mean albumin liver cirrhosis patients in previous studies obtained were 2.71 ± 0.74 g/dl, 2.8 ± 6 g/dl, 3.9 ± 0.7 g/dl, 3.02 ± 0.66 g/dl [11,14,17,19].

Albumin is synthesized in the liver. Decrease in albumin levels due to liver synthesis function decreased because the process of cirrhosis. Serum albumin levels can be used to assess the degree of severity of cirrhosis. Hypoalbuminemia is not specific for liver disease because it is also be caused by other factor like malnutrition.

Research on the population of hospitalized patients with end stage liver disease found the mean total bilirubin 1.5 (0.8 – 3.2) mg/dl, creatinine 1.0 (0.9 – 1.3) mg/dl, and INR 1.3 (1.1 – 1.5)[13]. Other studies reported bilirubin levels of 6.7 ± 9.0 mg/dl, creatinine 2.4 ± 1.5 mg/dL, INR 1.35 ± 0.35[11]. Creatinine levels of patients with liver cirrhosis 93.6 ± 67.5 µmol/L. Normal or low creatinine levels often occurred despite GFR already decreased[9].

In this study, the mean value of total bilirubin levels was increased. Increased bilirubin showed the severity of liver cirrhosis. Bilirubin level is an independent variable associated with the extent of fibrosis in liver cirrhosis. Increased serum bilirubin levels of 10 mg/l increase the probability of fibrosis expansion by 3.4 times (p=0.05, 95% CI 1.0 to 11.2). Increased average concentrations of bilirubin in this study also meant progression to severe liver cirrhosis due to expansion of fibrosis[23].

Most of the proteins associated with the process of coagulation is produced in the liver. Coagulopathy disorders associated with the severity of liver dysfunction[22]. Coagulopathy indicated by elongation of PPT that does not improve with treatment of vitamin K[24].

The mean score of MELD in this study was higher than a systematic review of research that showed patients with liver cirrhosis MELD score mean of 9.7 ± 9.2, median 9 (4-14) or a median of 12 (7-18)[13,10,15]. This indicated that the degree of severity of the subjects in this research to be heavier than subjects in the previous studies.

Average concentrations of cystatin C in this study was higher than the upper limit of the cystatin C used in this study (0.96 mg/l), which indicated the occurrence of renal abnormalities. Previous studies have found the mean cystatin C in patients with liver cirrhosis at 1.21 ± 0.41 mg/l and (1.13 ± 0.09 mg/l)[19,20]. The mean levels of cystatin C in liver cirrhosis patients with normal renal function was 1.07 ± 0.25 (0.71 to 1.68) mg/l, while in patients with decreased renal function was 1.81 ± 0.66 (1.03 to 2.99) mg/l[17].

Several studies have consistently shown that cystatin C at least as good as creatinine as a marker of function in the adult population and some studies have even shown that cystatin C had been more sensitive than creatinine against small changes LFG[25].

From table 2 it was found that gender did not differ significantly between groups of cystatin C >0.96 mg/l and ⩽ 0.96 mg/l. The average age was older in the group of cystatin C > 0.96 mg/l than in group with cystatin C ⩽ 0.96 mg/l but the difference was not statistically significant. This showed that the gender and age did not affect the levels of cystatin C. Cystatin C production is constant and not influenced by age, gender and muscle mass[5].

Ascites were more common in groups of cystatin C > 0.96 mg/l than the cystatin C ⩽ 0.96 mg/l, but this difference was not statistically significant (p=0.442). This was consistent with the results of the study which found that the edema and ascites did not affect the levels of cystatin C[26]. Renal impairment is rare in cirrhosis without ascites and very often at an advanced stage of cirrhosis with ascites and edema[1].

In this study, the mean score of MELD was higher in group with cystatin C > 0.96 mg/l than the cystatin C ⩽ 0.96 mg/l and this difference was statistically significant. This is consistent with a cohort study found that score of MELD is an independent factor of impaired renal function assessed by the increase in creatinine with a hazard ratio of 1.081 (p=0.007; 95% CI 1.041 to 1.123)[11].

In this study, the mean cystatin C was significantly different between MELD groups. This is consistent with studies that examined differences in average concentrations of cystatin C according to Child-Pugh groups, and found increased levels of cystatin C in patients with liver cirrhosis Child B

and C than Child A. There was no significant difference in cystatin C levels between Child B and C. A decline in renal function can already be found in Child A liver cirrhosis, although the results were not statistically significant[26]. The mean cystatin C was higher in patients with decompensated cirrhosis than compensated ones. Cystatin C is an excellent marker in assessing in the GFR and should be added as a routine examination of patients with cirrhosis of the liver to assess renal abnormalities[27].

Correlation test of cystatin C to score of MELD was significant with medium strength, with p=0.000 and r=0.485. The strength of this correlation is influenced by the distribution of subjects according to score of MELD which is relatively not even with MELD <10, 13 subjects (27.1%); MELD 10-19, 29 subjects (60.4%), MELD 20-29, four subjects (8.3%); and MELD 30-39 and > 40 respectively 1 subjects (2.1%). The result of linear regression showed that elevated levels of cystatin C were associated with increased severity of the liver, meaning that the greater the score of MELD the greater the level of cystatin C.

The severity of circulatory dysfunction has been reported to be associated with the severity of liver cirrhosis[28]. It was found that only score of MELD associated with cystatin C. Cystatin C levels between group score of MELD was significantly different. Score of MELD indicates the severity of liver cirrhosis, which also can be interpreted as circulation dysfunction. Severe circulatory dysfunction will eventually affect renal function as indicated by decrease in GFR. Decrease in GFR can be measured by an increase in cystatin C. Sex, age, albumin and ascites was not associated with increased levels of cystatin C or decreased renal function.

This study has several limitations. First, this study uses cross-sectional research design. Cross sectional study does not describe the course of the disease because of exposure and outcome measured at the same time so that no causal conclusion can be drawn. This can lead to bias due to existing data only describe the current state of research. Second, the distribution of subjects per group MELD scores was not even and thus affected the strength of correlation of cystatin C with a score of MELD. Third, although we have tried to control some possible disturbing factors that can affect cystatin C still there are several factors affecting levels of cystatin C which are not fully controlled, such as an increase or decrease in thyroid function (TSH and free T4 levels), the use of steroids high dose and the presence of malignancy (melanoma and colorectal cancer). Further research needs to be done with the design of case control or cohort study to find out whether cystatin C could be used as predictor of severity of liver cirrhosis.

CONCLUSION

There is a correlation between cystatin C levels with the degree of severity of liver cirrhosis according to score of MELD with medium strength.

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